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# The Influence of Some Epidemiological Factors and Clinical Presentation in the Survival of the Patients Diagnosed with pT1-T3 Renal Cell Carcinoma

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**Abstract:** ***Background**: According to the "European Network of Cancer Registries. Eurocim version 4.0", Renal Cell Carcinoma (RCC) is the most lethal genitourinary malignancy (1), with approximately 40% of the patients dying of metastatic disease progression (2). Based on, Cancer incidence and mortality patterns in Europe: estimates for 40 countries, in 2012 there were approximately 84,400 new cases of RCC and 34,700 kidney cancer-related deaths in the European Union (3). In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilized or declined thereafter. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend (4). Although there have been improvement in detection and treatment, there are still some uncertainties regarding the influence of some factors in the prognosis of the disease. **Objectives**: We evaluate how signs and symptoms altogether with some epidemiological factors such as: hematuria, flank pain, palpable tumor mass, thrombocytosis, haemoglobin level, erythrosedimentation rate (ESR), arterial hypertension (ATH), incidental diagnosis, smoking and gender influence in the prognosis of the patients diagnosed with Renal Cell Carcinoma, and treated with radical nephrectomy. **Material and methods**: Between January 2009 and January 2011, 123 patients were diagnosed with kidney tumors, out of them 96 patients were diagnosed with RCC, and were treated with Radical Nephrectomy at the Urology Service, University Hospital Center "Mother Teresa", Tirana, Albania. All patients included in the study were followed for up to 48 months. The duration of the follow- up was calculated from the date of the surgery to the death date or the last follow-up. The Kaplan-Meier analyzes, Cox model, and Log-rank test were used to calculate the mean survival time. **Results**: Out of a total of 123 patients with renal tumor, only 96 patients were diagnosed with RCC, and enter the study. The mean age of the patients was 59.5.6±11.24 years (range: 31-80yr), and male to female ratio was 1.28:1. The mean time of the follow-up was 44.6 ±1.3 months (range: 12-48 months). Fifty patients (52.1%) were diagnosed incidentally, during abdominal imaging examinations for other reasons. Only 6 patients (6.2%) had the classic triad (palpable renal mass + hematuria + flank pain) at the moment of diagnosis. Flank pain was the most frequent symptom, followed by hematuria, and palpable tumor mass (62.5%; 39.5%; 10.4% respectively). Follow-up time included in the study varied from 12 month to 48 months. During follow-up period 10 patients (10.4%) died from RCC. **Conclusions**: The study shows that"classic triad" is a strong prognostic factor in survival of patients treated with RN for RCC. Thrombocytosis and elevated ESR if present, correlates with worse prognosis.*

**Keywords:** Renal Cell Carcinoma, clinical presentation, classic triad, hemoglobin, elevated ESR, thrombocytosis, prognostic factor.

## 1. Introduction

Renal cell carcinoma represents 2-3% of all cancers. The "European Network of Cancer Register, Eurocim version 4.0 in 2001" found that the highest incidence of RCC was in Western countries (1). It is by far the most common malignant tumor of the kidney. Over the last two decades until recently, the incidence of RCC increased by about 2% both in Europe and worldwide. According to Levi F et al, in some European countries, over the past 10 years an upward trend of mortality rates was observed (4). The same trend regarding mortality rates during the last decade is observed in Albania too.

Janzen et al. in their publication noted that RCC is often detected incidentally on abdominal imaging, but even so, about 25% of patients with RCC have evidence of metastatic disease at presentation (5). Complete removal of the tumor is curative in the majority of patients, but about 30% ofpatients who undergo nephrectomy for localized RCCwill experience disease recurrence during their lifetime. Coppin et al, in a systematic database review found that the systemic immunotherapy for advanced RCC leads toonly a 15–30% response rate, with a smaller percentage ofpatients experiencing a durable, complete remission (6).The identification of factors that will predict the course ofthe disease and the response to current therapeuticagents should aid to optimize care for individual patients.

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular. Ficarra et al., in a retrospective analysis of 675 cases, concluded that many prognostic factors for survival have been identified in RCC, with tumor stage, age, and functional status being the most significant ones (7)

## 2. Material and Methods

Between January 2009 and January 2011, 123 patients underwent open radical nephrectomy for kidney tumors at the University Hospital Center "Mother Teresa", Tirana. Patients were diagnosed with kidney tumors, either based on their clinical signs and symptoms presented, or incidentally during imaging examinations for other reasons. All patients

included in this study diagnosed with kidney tumor, prior radical nephrectomy conducted an interview with a designated urologist, who, in turn, wrote down all the information in aspecial form that was prepared for this purpose. The majority of the patients were diagnosed incidentally. Clinical features studied included age at surgery, sex, signs and symptoms at presentation, comorbidities, and Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) (8). Type of surgical intervention lumbar, abdominal, or nephron sparing surgery was also included in the individual form. All pathological specimens were seen or examined by one urologic pathologist. Pathological features included TNM stage, histological subtype and tumor size based on WHO 2009 classification (9) with the improvements done in 2012 (10), Fuhrman nuclear grading system (11).

Vital status, laboratory, and imaging examinations for patients treated with radical nephrectomy were also recorded. The individual form was updated at periods of 3 moths, 6 months, 12 months, and then yearly for up to 48 months. Starting form the second year of the follow-up, if there was any absence or relapse of the disease, the time interval between routine clinical and imaging evaluation was increased to 6 months. The follow-up included full blood count, biochemistry laboratory examination, urinary system ultrasound, (CT and/or MRI, chest X-Ray examination) and ECOG-PS. Recurrence time and sites were recorded in the individual form, and was divided as local recurrence (lumbar fossa or retroperitoneal lymph nodes), carcinomas in the contralateral kidney, and distant metastases.

Patients diagnosed with benign kidney tumors or other kidney tumors except RCC, or kidney tumors affected both kidneys, or under chemotherapy treatment for other malignant disease, or other non-malignant diseases that could influence in the survival of the patients, and patients that refused surgical intervention were excluded from the study. All statistical tests were performed using SPSS 20.0 (Statistical Package for Social Sciences version 20.0)

## 3. Results

Out of all 123 patients who were the first to enroll in the study, 27 were excluded (3 patients have benign renal tumors, 3 patients were diagnosed with upper tract urothelial carcinoma, 2 patients have kidney tumors in both kidneys, 3 patients were under chemotherapy treatment for breast cancer, 4 patients have cardiac insufficiency grade III-IV, one patient refused radical nephrectomy, and 11 patients have missing information or data during follow-up period composed the group of excluded patients).

In this study the male/female ratio was 1.28:1. In addition, the mean age of the patients was 59.6 years ±11.24 (range: 31-80yr), while the mean age in the follow-up was 44.6 ±1.3 months (range: 12-48 months). Fifty patients (52.1%) were diagnosed incidentally without any signs or symptoms related to kidney tumors, while, in the meantime 6 patients (6.2%) had the "classic triad" (palpable tumor+hematuria+flank pain) at the moment of diagnosis. Fifty five patients (56.8%) had tumor located in the right kidney, while 41patients (43.2%) had it in the left kidney (see Table 1).

All the patients enrolled in the study underwent lumbar Radical Nephrectomy. Tumor size measured after Radical Nephrectomy was as follows: 13 patients had kidney tumor less than 4 cm in greatest dimension; in 37 patients tumor size was 4-7 cm in greatest dimension; in 22 patients tumor size was 7-10 cm, while in 24 patients tumor size was >10 cm (see Table 2).

Than by using Kaplan-Meier analyses, Cox models and Kendal's tau correlation coefficient, we calculate the impact on the patients' survival of different patient-related factors, such as gender, arterial hypertension (ATH), cigarette smoking, serum markers (Haemoglobin level, thrombocytosis, elevated ESR), and clinical presentation of the patient at the moment of diagnosis (patients presented with classic triad, and those diagnosed incidentally). Through binary logistic regression analyses we did not found any occasional relation statistically important between gender and death (OD=1.19; CI 95%= 0.56-2.21; see Table 3).

The median survival time of the patients without classic triad was (45.97 ±1.01 months) statistically ($p<0.001$) longer than the median survival time (12.5±4.5 months) of patients presented with all three symptoms of the classic triad (Kaplan-Meier analyses, Log rank test=47.73, df=1, $p<0.001$) (Table 4, and Figure1). There was a positive correlation between the presence of classic triad and death (Spearmen correlation coefficient: $r=0.553$, $p<0.001$). Also we found a negative correlation between survival time and presence of the classic triad (Spearmen correlation coefficient: $r=-0.318$, $p=0.012$; see Figure.2). This result showed that patients presented with classic triad have more probability to die earlier, and have shorter survival time those other patients that do not have classic triad as clinical presentation.

In Table 4 we summarize the relation between the survivals and different other biochemical parameters, using Kendal's tau correlation coefficient. The data showed that thrombocytosis ($r=0.396$, $p=0.007$), elevated ESR ($r=0.344$, $p=0.015$), and classic triad ($r=0.553$, $p<0.001$), have a significant relationship with patients' death. Amongst these factors, classic triad has the strongest statistically effect on patients death ($p<0.001$).

## 4. Discussion

Several potential prognostic factors have been implicated in the prognosis of the patients diagnosed with RCC treated with RN. This study shows that clinical presentation (classic triad) is a strong independent prognostic factor of survival in patients diagnosed with RCC (12). The majority of renal tumors remain asymptomatic until advanced disease develops due to retroperitoneal location of the kidneys. Local symptoms arise only after it achieves adequate size to displace or invade other organs. The classic triad is now detected in fewer than 10% of patients (13). Our study supports these findings, (classic triad was present in6.2% of patients). Nearly half of the patients presenting with all three

symptoms already suffer from metastatic disease. This is the reason why patients with classic triad had a very short survival time) compared to other group of patients who did not have all three symptoms. Pattard et al., have concluded that, the clinical presentation as an independent prognostic factor of RCC (14). Our results confirm what other publications have concluded that, classic triad could be considered as a strong prognostic factor that influences the survival of the patients diagnosed with RCC ($p<0.001$)(12,14).

Flank pain was the most frequent symptom in our study (62.5%), and it was caused by either bleeding within the tumor or invasion of contiguous tissue. In other publications this figure is up to 40% of patients. This discordance could be explained by the fact that not all flank pain recorded in our study was related to kidney tumor itself, but it may be of other origin, rheumatism or spine diseases etc. Hematuria, as symptom in our study was presented in 39.5% of cases, which is in line with other publications (15). Northway et al., observed that, palpable mass has been reported in one third of cases (16). We found palpable mass in 10.5% of patients included in the study. This figure could be explained either by a high percentage of incidentally diagnosed patients in the study (52.1% of cases), or because the majority of our patients diagnosed with RCC belonged to low stage disease groups pT1-pT2 (84 pt. out of 96pt: 87.5% of cases), with only 12 patients belonged to pT3 stage (see Table 2).

Gender did not reach any statistical significance on survival in our study (OD=1.19; CI 95%= 0.56-2.21), therefore it could not had any prognostic influence on the patient's survival. Most authors evaluating the impact of epidemiological factors in the prognosis of patients diagnosed with RCC, confirm this statement (17).

Biological parameters may be adversely related to the prognosis. Inflammation is frequent in RCC and ESRis elevated too. Our statistical results showed that patients with elevated ESR had worse prognosis compared with patients with normal ESR levels. Thrombocytosis is another factor that we found to have an influence in the survival of the patients diagnosed with RCC. Lang H and Jacqmin D, in their publication have concluded that: Only ESR can be considered as an independent factor that influence in the prognosis of RCC patients, and thrombocytosis is correlated with worse prognosis (18).

The other factors studied: arterial hypertension, incidental diagnosis, cigarette smoking, and low haemoglobin level did not reached any statistical difference that could influence the patients' survival so they could not be considered as prognostic factors. Lang H and Jacqmin D (18), cited above have concluded that patients with low haemoglobin level at presentation have worse prognosis. This discordance between our study and other studies may be explained by the fact that in our study, we do not have included patients with advanced T stage or metastatic disease (stage pT4, and M1 patients) that are prone to have low haemoglobin levels and worse prognosis as well.

## 5. Conclusion

Our study confirms that clinical presentation is a strong independent prognostic factor in the survival of patients diagnosed with RCC, after radical nephrectomy. Symptoms ("classic triad") are the most important factors. Thrombocytosis and elevated ESR if present, correlates with worse prognosis.

## 6. Conflicts of interests

The authors have nothing to disclose

## 7. Acknowledgments

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**Table1**: Epidemiological factors and clinical presentation

| Population characteristics | Patients no. (%) |
|---|---|
| Age (Years) | 59.6±11.24 (31-80) |
| Male/Female | 55/41(1.14/1) |
| Incidental diagnosis | 50 (52.1%) |
| Classic triad | 6 (6.2%) |
| Flank pain | 60 (62.5%) |
| Hematuria | 38 (39.5%) |
| Palpable tumor mass | 10 (10.4%) |
| Cigarette smoking | 10 (10.4%) |

**Table 2:** Distribution of patients by tumor size and T stage

| Tumor size | Patients no. |
|---|---|
| < 4cm | 13 |
| 4 – 7 cm | 37 |
| 7 – 10 cm | 22 |
| >10 cm | 24 |
| **T stage** | |
| pT1 | 43 |
| pT2 | 41 |
| pT3 | 12 |

**Table 3:** Binary logistic regression between analyses between gender and death

| Gender | Alive (n=86, 89.6%) | Dead (n=10, 10.4%) | OD | CI 95% |
|---|---|---|---|---|
| *m* | 48 (55.6) | 7(66.7) | 1.19 | 0.56-2.21 |
| *f* | 38 (44.4) | 3 (33.3) | reference | |

**Table 4:** Correlation between different epidemiologic and patient-related factors on the patients' survival (Kendal's tau correlation coefficient)

| **Correlation between different factors and survival** | | |
|---|---|---|
| **Variables** | **r*** | **p value** |
| Classic triad | 0.553 | **<0.001** |
| Thrombocytosis | 0.396 | **0.007** |
| Low haemoglobin level | 0.182 | 0.198 |
| ESR (elevated) | 0.344 | **0.015** |
| Hypertension | 0.236 | 0.095 |
| Cigarette smoking | 0.252 | 0.074 |
| Incidentally diagnosed | 0.115 | 0.418 |

***Kendal's tau coefficient**

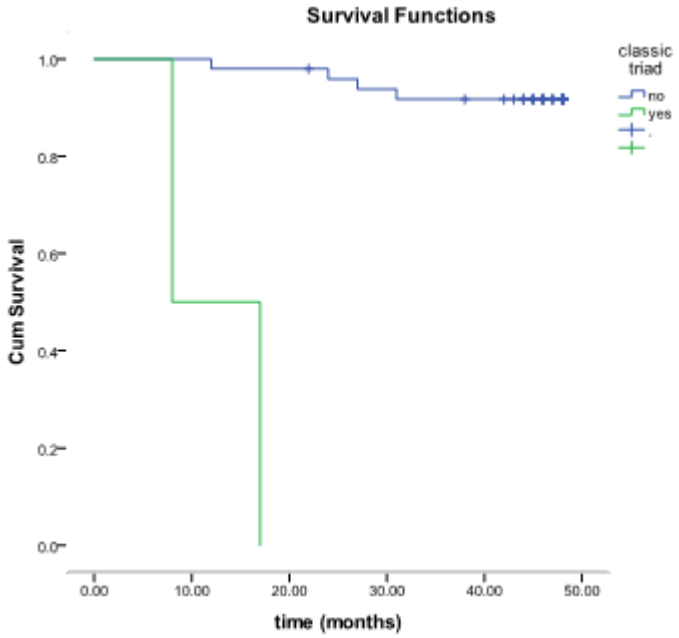


**Figure1:** Kaplan-Meier estimated median survival for different clinical presentation; classic triad vs no classic triad

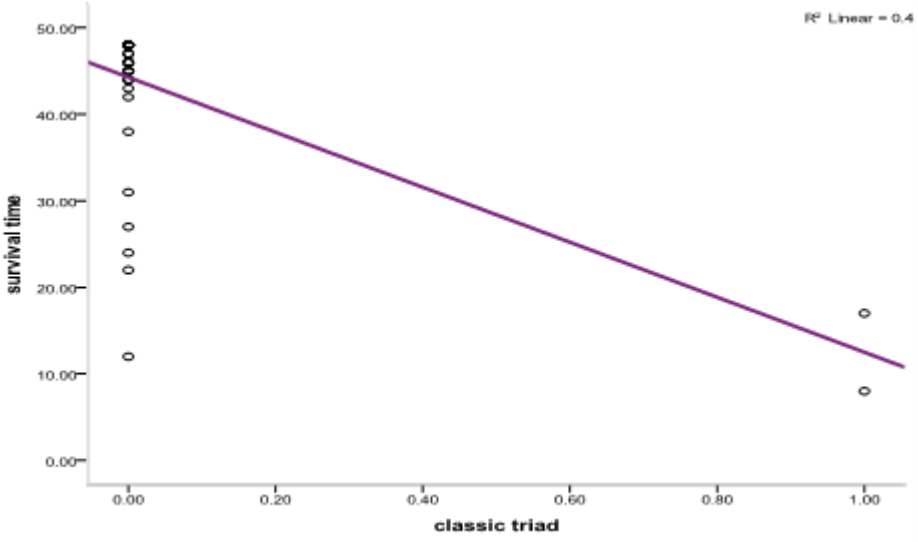


**Figure 2:** Correlation between survival time and classic triad